REMARKS

The present amendment is responsive to the Office Action mailed November 13, 2006. Applicant submits concurrently herewith: (1) a Petition for Extension of Time for three months up to and including Sunday, May 13, 2007; (2) Exhibit A: copy of page 264 of *Five-Lipoxygenase Products in Asthma*, Drazen, Dahlâen and Lee, eds., Published 1998, Marcel Dekker, Inc., New York; and (3) an Information Disclosure Statement.

Claims 1-15 were pending in the application. In the Office Action, claims 1-15 have been rejected. In the instant Amendment, claims 1, 3-5, 7-9, 11 and 13-14 have been amended, and new claims 16-19 have been added. Thus, upon entry of the instant Amendment, claims 1-19 will be pending in the application.

Claims 1 and 11 have been amended to recite that step (a) involves mixing a "particulate" carrier with a first portion of a first particulate inhalant medicament to form a first mixture, wherein "said particulate carrier has a volume median diameter (VMD) of from about 50 to about 250 μm." Claim 11 has also been amended to recite that the dry powder inhalation composition "consists of said particulate carrier, said first particulate inhalant medicament and said second particulate inhalant medicament." Support for the amendatory language is found in the specification, *e.g.*, in page 5, paragraph [0016]; page 6, paragraph [0020]; and pages 10-12, Example 1.

Claims 3-5 have been amended to maintain proper antecedent basis. Claims 7-9 and 13-14 have been amended to correct typographical or editorial errors.

New claims 16-19 have been added. Support for claim 16 is found in the specification, *e.g.*, page 5, paragraphs [0016]; and pages 10-12, Example 1. Support for claims 17-19 is found in the specification, *e.g.*, in page 6, paragraph [0020].

Thus, no new matter has been added by these amendments. Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

Claim 13 has been objected to in connection with the recitation of "dehydrate". Applicant has amended claim 13 to correct the misspelling. The objection is therefore obviated, and should be withdrawn.

Claim 14 has been objected to under 37 C.F.R. 1.75(c) as being in an improper form. Applicant has amended claim 14 such that it refers to other claims in the alternative. The objection is therefore obviated, and should be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 6-9, 12 and 14-15 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on the ground that the recitation of "derivatives" is unclear because it is not defined with respect to anti-inflammatory steroids or bronchodilators.

Applicant respectfully submits that a person skilled in the art would readily appreciate and understand the meaning of the term "derivative" used in the context of an anti-inflammatory steroid such as budesonide or a bronchodilator such as formosterol. Applicant respectfully directs the Examiner's attention to the following extant publications that use the term: U.S. Patent 5,712,263 (see, *e.g.*, Abstract; steroid derivatives), U.S. Patent 5,434,304 (see, *e.g.*, Abstract,

formosterol derivatives), and *Five-Lipoxygenase Products in Asthma*, Drazen, Dahlâen and Lee, eds., Published 1998, Marcel Dekker, Inc., New York, page 264; budesonide derivatives; submitted herewith as Exhibit A). These publications illustrate that a person skilled in the art would understand the term as it is used in the present context. The rejected claims are therefore not indefinite. The rejection of claims 6-7, 12 and 14-15 should be withdrawn.

THE REJECTIONS BASED ON ANTICIPATION

Claims 11 and 13-14 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Keller, *et al.*, WO 00/28979 using U.S. Patent 6,645,466 as the English language equivalent (hereinafter "*Keller*"). The Examiner contends that *Keller* teaches a dry powder composition with improved moisture resistance consisting of 0.2% w/w formoterol fumarate dehydrate (2^{nd} medicament), 0.5% w/w glycopyrrolate (1^{st} medicament), 0.5% w/w magnesium stearate (excipient), and 98.8% w/w of lactose monohydrate (carrier), and that the constituents in its dry powder composition can be mixed with one another in any desired sequence.

Applicant respectfully submits that the rejected claims, as amended, exclude the presence of magnesium stearate. Thus, *Keller* does not anticipate the dry powder composition of claims 11, 13 and 14. Withdrawal of the rejection is respectfully requested.

Claims 11-15 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Trofast, *et al.*, U.S. Patent 6,030,604 (hereinafter "*Trofast*"). The Examiner contends that *Trofast* teaches a dry powder composition comprising 5.2 parts of formoterol fumarate dehydrate, 896.8 parts of lactose

monohydrate (carrier), and 98 parts of budesonide, wherein the lactose and formoterol are mixed, micronized, and treated according to the method of WO 95/05805, budesonide is added, and the mixture is remixed, remicronized, and agglomerated.

Trofast teaches micronizing its dry powder composition after the active ingredients are mixed with the carrier. *Trofast* also teaches that as a result of the micronization, all ingredients, including the carrier, are rendered less than 10 μm in size (*see, e.g., Trofast*, col. 2, lines 3-10 and 50-58). *Trofast* dose not teach a dry powder composition consisting of a particulate carrier having a volume median diameter (VMD) of from about 50 to about 250 μm, a first particulate inhalant medicament and a second particulate inhalant medicament. Thus, *Trofast* does not anticipate claims 11-15. Withdrawal of the rejection is respectfully requested.

THE REJECTION BASED ON OBVIOUSNESS

Claims 1-10 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Trofast* in view of *Keller*. The Examiner contends that although *Trofast* does not teach the order of steps used in preparing the dry powders, this deficiency is cured by *Keller*. Claims 1, 5-8, and 11-14 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over *Walz*, et al., U.S. RE 38,912 (hereinafter "*Walz*") in view of *Keller*. The Examiner contends once again that although *Walz* does not teach the order of steps used in preparing the dry powders, this deficiency is cured by *Keller*. Applicant respectfully submits that neither rejection sets forth a *prima facie* case of obviousness.

Trofast and *Keller* have been discussed above. *Walz* teaches a method of preparing a dry powder composition by a so-called layered mixing process in which an excipient with an average

larger particle size and an active substance with an average smaller particle size are placed in a mixing vessel in alternating layers (see, *Walz*, col. 1, lines 58-63). After all layers have been placed, a mixing step is undertaken so that the components are mixed (see, *Walz*, col. 1, lines 63-65). *Walz* asserts that its method represents an improvement over the conventional method involving multistep mixing (see, *Walz*, col. 1, lines 31-45). *Walz* teaches that powders having more than one active ingredient can be produced by first placing different ingredients in different layers, then mixing all ingredients in one mixing step (see, *Walz*, col. 6, lines 10-30). Thus, notwithstanding the initial layering, *Walz*'s method uses a single "mixing" step.

Keller does not teach or suggest dividing one of the medicaments into separate portions and mixing them at different times with the other medicament and the other ingredients to produce a dry powder composition. The Examiner contends that *Keller* teaches that the different ingredients can be mixed in any desired sequence, and thus "encompasses" the claimed step sequences. To support the contention, the Examiner cites the following teachings in *Keller*:

> [i]n principle, the constituents can be mixed with one another in any desired sequence, where, however, mixing should expediently be carried out in such a way that the particles of the constituents--apart from the adhesion to the carrier particles--are essentially retained as such, i.e. are not destroyed, for example, by granulation and the like.

Keller, at col. 8, lines 53-59. Applicant respectfully points out that from the context of the paragraph, the cited teachings concern the preparation of a dry powder composition that contains one active ingredient, magnesium stearate (which is not an active ingredient but an excipient), and the carrier (see the

statement in *Keller* immediately before and after the cited statements, at col. 8, lines 46-53 and lines 59-65). Thus, *Keller* teaches that the active ingredient, magnesium stearate and the carrier can be mixed in any order. Such a teaching does not teach or suggest anything about the sequence of mixing two different active ingredients with the carrier. A dry powder composition that comprises two active ingredients is disclosed in Example 8 in *Keller*. However, Example 8 provides no teaching of the step sequence in which the two active ingredients are mixed with the carrier. Instead, Example 8 refers to Example 4 for the method of preparation of the dry powder, which discloses the preparation of a dry powder composition having a single active ingredient, magnesium stearate, and a carrier by mixing the carrier with magnesium stearate first to form a mixture and mixed the mixture with the active ingredient. Thus, *Keller* does not teach or suggest any sequence of mixing two active ingredients, much less the sequence as claimed, *i.e.*, mixing a portion of the first active ingredient with the carrier, adding thereto and mixing the second active ingredient, and then adding thereto and mixing the rest of the first active ingredient. Besides, regardless of whether the above-quoted teaching in *Keller* could be said to "encompass" the claimed sequence, mere encompassing does not satisfy the legal criteria for establishing obviousness. Thus, *Keller* does not cure the deficiency in *Trofast* or *Walz*.

Applicant also respectfully submits that *Trofast* teaches a method of preparing a dry powder composition in which lactose and formoterol are mixed, micronized, and treated, budesonide is then added, and the mixture is remixed, remicronized, and agglomerated. Thus, in *Trofast*'s method, all ingredients, including the carrier, are rendered less than 10 μm in size. In the presently claimed invention, on the other hand, the

particulate carrier has a volume median diameter (VMD) of from about 50 to about 250 μm. The combination of *Trofast* and *Keller* does not teach or suggest the presently claimed method. In order to arrive at the presently claimed invention, a person of ordinary skill in the art would have had to modify *Trofast* to eliminate the micronization step. There is no evidence of record of this effect. Furthermore, it would appear that any advantages afforded by changing the sequence of mixing in *Trofast* would have been negated by the subsequent micronization.

Likewise, a person of ordinary skilled in the art would not have been motivated to modify *Walz*'s method by performing the mixing in accordance with the presently claimed invention, particularly since *Walz* asserts that its method represents an improvement over the conventional method involving multistep mixing. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, … would be led in a direction divergent from the path that was taken by the applicant. *See, Tec Air, Inc., v. Denso Manufacturing Michigan Inc*, 192 F.3d 1353, 1360 (Fed. Cir. 1999).

In an attempt to establish a motivation to produce the claimed invention, the Office Action contends that a person skilled in the art would have been motivated to combine the teachings of *Trofast* or *Walz* with *Keller* to obtain dry powder formulations comprising betamimetics for improved moisture resistance (see the Office Action at page 9, last paragraph, and page 12, last paragraph). However, as discussed above, *Keller* teaches that improved moisture resistance is achieved by adding magnesium stearate, not by choosing the sequence of mixing of active ingredients. Thus, the motivation advanced by the Examiner would still not lead to the presently claimed invention.

In view of the foregoing, Applicant respectfully submits that the determination of obviousness has been a result of hindsight reconstruction by picking and choosing among isolated disclosures in the prior art, and discounting or ignoring others, to deprecate the claimed invention. Using the inventor's disclosure as a blueprint, only selective teachings from *Trofast*, *Walz* and *Keller* have been relied upon to establish obviousness. The Federal Circuit has held:

> [t]o prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, *the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed*.

In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998) (emphasis added). In the present case, these requirements have not been satisfied.

Withdrawal of the rejection is respectfully requested.

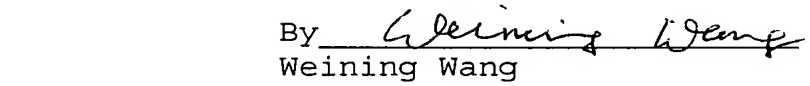
As it is believed that all of the rejections set forth in the Office Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Patent Office is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: May 14, 2007

Respectfully submitted,

By 

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cause a reduction in pulmonary mast cells with chronic administration. The net effect is a reduction of the local concentration of mast cell mediators in the airways. Similarly, steroids inhibit adherence and chemotaxis of eosinophils ex vivo without affecting the ability of these cells to synthesize LTC_4 after stimulation with ionophore.

Several studies have examined the effects of steroid administration on urinary LTE_4 excretion in both healthy volunteers and asthmatics. In two studies in healthy subjects (143,144) the administration of dexamethasone (8 mg/day for 2 days), inhaled budesonide (1.6 mg/day for 7 days), or prednisolone (60 mg/day for 7 days or 30 mg/day for 3 days) had no effect on urinary LTE_4 excretion. However, budesonide did reduce ex vivo thromboxane generation in zymosan-stimulated peripheral monocytes, and prednisolone administration decreased all eicosanoids in macrophage-rich BAL cells, suggesting a possible effect on arachidonate metabolism in these cells. Two additional placebo-controlled studies in asthmatics evaluated the modulating effect of chronically administered steroids on the allergen-invoked rise in urinary LTE_4 excretion. In the first (I.K. Taylor, unpublished data), pretreatment for one week prior to allergen challenge with 1.6 mg/day of budesonide derivatives attenuated the early and late allergen-induced bronchoconstriction without decreasing urinary LTE_4 excretion. In the second study (145), inhalational administration of 1 mg/day fluticasone dipropionate for 2 weeks prior to allergen challenge predictably reduced baseline airway reactivity, acute allergen-induced hyperreactivity, and early- and late-phase bronchoconstriction. Similar to the first study, steroid treatment had no inhibitory effect on the allergen-induced increase in urinary excretion of LTE_4. These in vivo data complement the ex vivo data and suggest that the disease modifying anti-inflammatory properties of the steroids relate to their modulation of cytokine networks rather than a direct action upon the metabolism of arachidonic acid.

Mechanistic strategies for inhibition of leukotriene synthesis have included inhibition of 5-lipoxygenase–activating protein (FLAP) or inhibition of 5-lipoxygenase. The activation of both enzymes are required for leukotriene synthesis in vivo (146,147). Although clinical trials utilizing FLAP inhibitors have been discontinued, early studies with MK-886 (148) and MK-0591 (149) showed that these drugs were effective in decreasing early and late allergen-induced bronchoconstriction as well as decreasing urinary LTE_4 excretion. However, the FLAP inhibitors were ineffective in attenuating the allergen-induced airway hyperresponsiveness.

Early efforts to examine the efficacy of 5-lipoxygenase inhibitors failed to show any therapeutic benefit (150–152), but they also failed to provide evidence of adequate enzyme blockade. Two recent studies have also failed to find beneficial effects of 5-lipoxygenase inhibitors (153,154). Both studies used only a single administration of inhibitor (zileuton or ZD2138) given 3–4 hours prior to allergen challenge, and both studies reported a 50% decrease in urine LTE_4 con-